How Is Epidemiology Used in Risk Management Planning and Safety Assessment?

Epidemiology in the pharmaceutical industry

Epidemiology is the study of the distribution in specified populations of health-related states or events, including the factors that influence their occurrence, and the application of this study to the control of disease and other health problems. Epidemiology contributes to the success of several important functions within a pharmaceutical company, including product planning and the development of medicines, but its greatest contribution is in the area of medicine safety evaluation.

The safety profile of any medicine reflects an evolving body of knowledge, extending from preclinical studies of a potential medicine to its first use in humans and then through the post-approval life cycle of the medicine. Pre-approval clinical studies and post-approval spontaneous reporting are important in assessing medicine safety, but there are many relevant safety issues that can only be studied through observational epidemiology such as:

- Estimating the incidence of, and risk factors for, rarely occurring events in large populations exposed to a medicine.
    - For example, whether the risk of cardiac adverse events is greater in one type of medicine used to treat a specific disease compared with another type of medicine used to treat the same disease
- Studying events with a long latency period.
    - For example, decreased bone mineral density (associated with increased risk of fracture) in adults who had previously received medicinal therapy for a serious childhood illness.
- Studying cross-generational effects of a drug.
    - Since pregnant women are generally excluded from clinical studies for ethical reasons, the effects of many medicines on a human pregnancy are not well known. Epidemiologic methods have been used to examine possible associations between medicines and birth defects. Pregnancy registries have been set up for medicines that are essential to take even during pregnancy (e.g., HIV medications, epilepsy medicines) to enable pregnancy outcomes to be monitored prospectively and provide information on which patients and their health care providers can make informed treatment decisions.

While observational epidemiology offers some advantages, information from epidemiology studies should never be viewed in isolation from other data sources when addressing questions about a medicine's safety. Results from clinical studies, spontaneous reports, epidemiology studies, and where relevant, preclinical datasets, should all be evaluated for their potential to address the particular safety question raised, taking into account the unique strengths and limitations of the study designs and data collection methods used.

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Pre-approval epidemiology studies

Descriptive epidemiology studies conducted before a medicine is approved are useful for:

- Establishing how frequently risk factors and coexisting illnesses occur among patients expected to use the new medication.
- Identifying patterns of health care utilization and prescribing of currently approved treatments.
- Quantifying background rates of mortality and serious nonfatal events.

With the wide availability of computerized health databases, it is now possible to conduct studies across diverse patient populations (e.g., private/public assistance insurance or varying geographical areas) and compare disease rates, examining the effect of differences in clinical practice or access to health care. When these data are available prior to approval, background rates of mortality and morbidity are useful to place the incidence of adverse events observed in Phase 3 clinical studies in perspective. These data also provide the "real-world" estimates necessary to design feasible post-approval studies.

Post-approval epidemiology studies

Randomized clinical studies conducted during the pre-approval phases of medicine development often have strict eligibility criteria to identify appropriate participants and avoid situations where factors such as other medical conditions or concomitant medications might make it difficult to interpret the study results. In addition, these study subjects include at most a few thousand patients in total, which is sufficiently large to provide evidence of a beneficial effect on a disease or condition and to exclude large increases in risk of common adverse events. However, pre-approval studies are rarely large enough to detect small differences in the risk of common adverse events or to reliably estimate the risk of rare events. Identification and quantification of potentially infrequent but serious risks require larger studies that are designed to distinguish between the role of background risk factors and the effects of a particular medicine on the rate of outcomes. Descriptive epidemiology studies can also be conducted post-approval to describe the characteristics of the users of a new medicine and the patterns of use of the medicine, and may also provide measurements of the drug's effectiveness at the population level.

Regulators and the medical community have communicated a desire for safety data from the populations that will actually use the drugs in "real-world" clinical practice settings. This had led to a greater emphasis on the use of observational methods to understand the safety profile of new medications after they are marketed.

For more information, visit the International Society for Pharmacoepidemiology (ISPE) at *http://www.pharmacoepi.org/about/index.cfm*.

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Observational epidemiology study designs

Observational study designs are frequently used to study the safety of medicines because these treatments are assigned by real-world clinicians rather than by experimental design. Thus, these studies seek to understand safety based on how physicians and patients use medicines in real-world settings. Studies can use prospective or retrospective approaches:

- In a prospective study the collection of data is planned in advance.
- A retrospective study is conducted using data that were collected before the research question was conceived.

Epidemiologists use different designs depending on the research question.

- **Cross-sectional studies**, also called prevalence studies, are studies in which information (e.g., characteristics, experiences, or behaviors) is collected about exposures, outcomes, and other characteristics of interest at the same time. This allows estimation of the prevalence of disease, exposure to medicines, and other factors in a defined population. It does not, however, permit the researcher to know if a factor caused an outcome.
- **Case-control studies** typically involve the retrospective analysis of people with an adverse event (cases) and people without an adverse event (controls) to identify factors (e.g., exposure to a medicine) that are more frequent in cases than controls. Sometimes, the control group is matched by demographic characteristics (e.g., age, gender, race, diseases, concomitant medications, etc.), but the most important factor is that the cases and controls arise from the same underlying population. The data are then analyzed to determine whether the odds of patients experiencing a specific adverse event were higher if they received the medicine being studied (see next page).
  - A nested case-control study is when cases and controls are drawn from a prospective or retrospective cohort study.
  - Case-crossover studies are a specialized study type designed to study the transient effect of brief or irregular exposures on the occurrence of a rare, acute-onset disease. Patients in this design serve as their own controls by comparing exposed and unexposed time periods of each patient.
- **Cohort studies** seek to determine how individuals' personal characteristics may affect their likelihood of developing an adverse event (AE). Participants are followed over time to see if they develop the AE being studied. A cohort is a group within the study that shares a common characteristic within the relevant time period. The relative risk of developing the AE can be calculated for patients who received a particular medicine compared with those who did not (see next page). These studies may be conducted prospectively (e.g., The Women's Health Study of female health professionals in the U.S.) or retrospectively (e.g., by using large electronic health care databases).
- **Large simple trials** are those in which large numbers of patients are randomly assigned to a treatment and then followed observationally. The randomization controls for confounding patient factors (that might affect both their risk for an adverse event and their likelihood of being assigned to a particular treatment). The large study size can help make it possible to evaluate small risks. The simplicity of the study procedures (e.g., inclusion/exclusion criteria, use of concomitant medication, frequency of patient monitoring) approximates real-world clinical practice.

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Calculating Risk Statistics

Relative and Absolute Risk

Suppose that in a **cohort study**:

Of 10,000 patients who received medicine X:

- 35 experienced event A
- 9,965 did not experience event A

Of 10,000 patients who did *not* receive medicine X:

- 15 experienced event A
- 9,985 did not experience event A

The data can be presented in a 2x2 table:

Experienced Event A?	Received Medicine X? Yes	Received Medicine X? No
Yes	35	15
No	9,965	9,985

Relative Risk: The relative risk of experiencing event A is the rate in patients exposed to the drug divided by the rate in the unexposed, or 35/10,000 divided by 15/10,000 = 2.3. This means that a person who is exposed to the medicine is 2.3 times as likely as an unexposed person to experience the event.

Any value for relative risk of >1 may suggest an association between a medicine and an adverse event. Values <1 may suggest a preventive association. However, a potential association will frequently require further study before it can be confirmed.

Absolute Risk: The excess risk, or absolute risk difference, in the example above, is 35/10,000 minus 15/10,000, or 0.002. This means that for every 1,000 patients treated with the medicine, 2 additional patients will experience event A.

Odds Ratio

Suppose that in a **case-control study**:

Of 100 patients who experienced event A:

- 30 took medicine X
- 70 did not take medicine X

Of 100 patients who did *not* experience event A:

- 10 took medicine X
- 90 did not take medicine X

The data can be presented in a 2x2 table:

Received Medicine X?	Experienced Event A? Yes	Experienced Event A? No
Yes	30	10
No	70	90

Odds Ratio: This is the odds of experiencing event A for patients exposed to medicine X (30:10) divided by the odds of experiencing event A for patients unexposed to medicine X (70:90):

$$\frac{30:10}{70:90} = \frac{30 \times 90}{10 \times 70} = \frac{27}{7} = 3.9$$